REMARKS

Claims 1-3, 5-12, and 38-45 were pending in this application. Claims 5, 9, and 38-44 have been cancelled and claims 1, 2, 3, 6, 7, 8, and 45 have been amended. Accordingly, claims 1-3, 6-8, 10-12, and 45 will remain pending in the application upon entry of the claim amendments presented herein. For the Examiner's convenience, a copy of the claims that will be pending upon entry of the amendments presented herein is attached hereto as Appendix B.

Support for the amendments to the claims may be found throughout the specification, including the originally filed claims. *No new matter has been added.*

Attached hereto is Appendix A titled "Version with Markings to Show Changes Made," which indicates the specific amendments made to the specification and the claims.

Amendment of the claims should in no way be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or one or more separate applications.

Rejection of Claims 1-3, 5-12, and 45 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-3, 5-12, and 45 under 35 U.S.C. 112, first paragraph, because, according to the Examiner,

> the specification, while being enabling for a method of determining a predisposition to narcolepsy in canines by detecting a deletion of exon 4 or exon 6 of the hypocretin 2 receptor or to a method for determining a predisposition to narcolepsy in humans by detecting decreased levels of hypocretin 1 ligand as compared to the level of hyopcretin 1 in a normal control, does not reasonably provide enablement for detecting a predisposition to any disorder in any subject caused by any alteration in hypocretin receptor activity by analyzing nucleic acid from a subject to detect the presence of at least one polymorphism that predisposes the subject to a disorder caused by an alteration in activity of any hypocretin receptor, or methods dependant therefrom wherein the disorder is any sleep disorder or any sleep disorder that is characterized by increased wakefulness or decreased wakefulness, or wherein the disorder is any mood disorder, chronic fatigue syndrome, or attention deficit disorder, or wherein the individual is human or canine, or detecting any polymorphism within a genomic region between markers 26-8 and 530-3 of canine chromosome 12, or any truncated HCRtr2 transcript.

Applicants respectfully traverse the foregoing rejection. However, in order to expedite prosecution of the instant application, and in no way acquiescing to the Examiner's rejection, Applicants have amended claim 1, thereby obviating the foregoing rejection. Applicants reserve the right to pursue the claims as originally filed in this or one or more separate applications.

As amended, claim 1 is directed to a method for detecting a predisposition to a sleep disorder in a subject, the method comprising analyzing nucleic acid of a subject for the presence of at least one polymorphism in a hyopcretin receptor-2 gene, where the polymorphism causes an alteration in activity of a hypocretin receptor encoded by the gene; and where the presence of the polymorphism is indicative of a predisposition to the sleep disorder.

Applicants respectfully submit that the teachings in the specification clearly enable one of ordinary skill in the art to make and/or use the claimed invention. Applicants submit that Applicants' specification contains ample teaching of how to make and use the claimed invention, as well as working examples which describe the identification of the polymorphisms used in the methods of the invention.

Applicants have shown in both canines and in humans that a defect in the hypocretin system is associated with sleep disorder. If this system is disrupted (*e.g.*, due to, for example, a defect in the hypocretin receptor, or a defect in the hypocretin ligand), then the subject is likely to suffer from a sleep disorder such as narcolepsy. Applicants' specification describes several polymorphisms which are associated with sleep disorders in both canines and humans. In canines, which are an animal model for sleep disorders in humans, Applicants showed that an exemplary polymorphism of interest is an alteration in the hypocretin receptor 2 (Hcrtr2) sequence that affects production of a full-length functional polypeptide. See, *e.g.*, page 22, line 16 to page 26, line 9, and Examples 1-2 (page 42, line 23 to page 56, line 11). In humans, Applicants specification teaches that an exemplary polymorphism of interest is an alteration in the hypocretin ligand sequence. See, *e.g.*, page 27, line 1 to page 28, line 4, and Examples 5-6 (page 60, line 4 to page 68, line 12).

The term "polymorphism", while encompassing single nucleotide polymorphisms (SNPs), are not limited to such. Polymorphisms associated with sleep disorders can include any alteration in a nucleic acid sequence that leads to production of a hypocretin ligand or hypocretin receptor that does not function properly. Examples include alterations in the genomic sequence

(*e.g.*, within the non-coding region) that lead to alternative splicing and production of a hypocretin receptor that is truncated relative to wild-type, alternations that affect the coding sequence so as to affect interaction of the hypocretin ligand with its receptor, and the like.

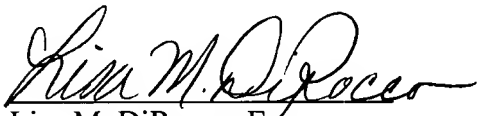
The invention further provides detailed teachings, including probes and primers which may be used for detection of a predisposition to a sleep disorder based on detection of a polymorphism which causes an alteration in activity of a hypocretin receptor (see *e.g.*, page 18, line 15 through page 28, line 4 of the instant specification).

Applicants thus submit that once provided with the teachings and guidelines of the present invention as disclosed in the specification, the procedures for carrying out the claimed invention become routine to one skilled in the art. As stated by the Board, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex Parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. Applicants submit that they have provided more than ample support for the presently claimed methods to enable one skilled in the art to practice the claimed invention. Applicants therefore request withdrawal of the instant §112, first paragraph, enablement rejection.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Dated: **Febraury 28, 2003**

APPENDIX A

VERISON WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please cancel claims 5, 9, and 38-44, without prejudice and amend claims 1, 2, 3, 6, 7, 8, and 45 as follows:

1. **(Amended)** A method for detecting a predisposition to a sleep disorder in a subject [caused by an alteration in hypocretin receptor activity], the method comprising:

analyzing nucleic acid of a subject for the presence of at least one polymorphism in a hyopcretin receptor-2 gene [that predisposes the subject to a disorder caused by], wherein the polymorphism causes an alteration in activity of a hypocretin receptor encoded by the gene;

and wherein the presence of the [predisposing] polymorphism is indicative of [an increased susceptibility of the subject to] a predisposition to the sleep disorder [caused by an alteration in a hypocretin receptor activity].

2. **(Amended)** The method of claim 1, wherein the [predisposing] polymorphism is in [a] exon 4 of the hypocretin receptor-2 gene.

3. **(Amended)** The method of claim 1, wherein the [predisposing] polymorphism is in [a] exon 6 of the hypocretin receptor-2 gene.

6. **(Amended)** The method of claim [5] 1, wherein the [predisposing] polymorphism [causes] in indicative of a sleep disorder characterized by decreased wakefulness.

7. **(Amended)** The method of claim [5] 1, wherein the [predisposing] polymorphism [causes] in indicative of a sleep disorder characterized by increased wakefulness or insomnia.

8. **(Amended)** The method of claim [5] 1, wherein the disorder is narcolepsy.

45. **(Amended)** The method of claim 11, wherein the polymorphism [is] encodes a truncated HCRtr2 transcript.

APPENDIX B

1. A method for detecting a predisposition to a sleep disorder in a subject, the method comprising:

analyzing nucleic acid of a subject for the presence of at least one polymorphism in a hypocretin receptor-2 gene, wherein the polymorphism causes an alteration in activity of a hypocretin receptor encoded by the gene;

and wherein the presence of the polymorphism is indicative of a predisposition to the sleep disorder.

2. The method of claim 1, wherein the polymorphism is in exon 4 of the hypocretin receptor-2 gene.

3. The method of claim 1, wherein the polymorphism is in exon 6 of the hypocretin receptor-2 gene.

6. The method of claim 1, wherein the polymorphism in indicative of a sleep disorder characterized by decreased wakefulness.

7. The method of claim 1, wherein the polymorphism in indicative of a sleep disorder characterized by increased wakefulness or insomnia.

8. The method of claim 1, wherein the disorder is narcolepsy.

10. The method of claim 1, wherein the subject is human.

11. The method of claim 1, wherein the subject is canine.

12. The method of claim 11, wherein the polymorphism to be detected is within a genomic region between markers 26-8 and 530-3, inclusive, of canine chromosome 12.

45. The method of claim 11, wherein the polymorphism encodes a truncated HCRtr2 transcript.